

**National Institutes of Health
National Institute of Allergy and Infectious Diseases
Division of Acquired Immune Deficiency Syndrome
AIDS VACCINE RESEARCH WORKING GROUP**

**May 27-28, 2004
Fernwood Building, Bethesda, MD**

MEETING SUMMARY

The AIDS Vaccine Research Working Group (AVRWG) met in public session on May 27 and 28, 2004, in Conference Room 2C-13 of the Fernwood Building, 10401 Fernwood Drive, Bethesda, MD 20892-4812.

AVRWG members present: Barton Haynes (chair), Deborah Birx (ex officio), James Bradac (executive secretary), Lawrence Corey (ex officio), Emilio Emini, Karen Goldenthal (ex officio), Alan Greenberg (ex officio), Scott Hammer, Eric Hunter, Bette Korber, John Moore, Gary Nabel (ex officio), Neal Nathanson, Douglas Richman, Jerald Sadoff, Steven Wakefield, and David Watkins.

NIH personnel participating:

- Margaret Johnston, Director, Vaccine and Prevention Research Program (VPRP), Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID);
- Jorge Flores, Chief, Vaccine Clinical Research Branch, VPRP, DAIDS;
- Richard Koup, Chief, Immunology Laboratory, Vaccine Research Center (VRC), NIAID;
- Bonnie Mathieson, Office of AIDS Research, NIH;
- Edmund Tramont, Director, DAIDS, NIAID.

Other presenters:

- Juliana McElrath, Professor of Medicine, University of Washington, and Member, Fred Hutchinson Cancer Research Center;
- José Esparza, Coordinator, HIV Vaccine Initiative, WHO-Joint U.N. Program on HIV/AIDS, and Director, Global HIV Vaccine Enterprise, Bill and Melinda Gates Foundation;
- Robin Isaacs, Senior Director, Infectious Disease-Clinical Research, Merck & Co., Inc.;
- Judith Wasserheit, Director, HIV Vaccine Trials Network (HVTN), Fred Hutchinson Cancer Research Center.

Opening Remarks

Dr. Haynes asked members to review the minutes of the January 2004 meeting, which will be posted to the AVRWG website when approved. He also solicited topics for the AVRWG meeting on September 1, 2004, in conjunction with the AIDS Vaccine Conference in Lausanne, Switzerland. Among the topics suggested by members were immunogen design, vectors, clinical

trials, and animal models. Future meetings of AVRWG will be January 12-13 and May 25-26, 2005. Dr. Haynes also asked members to disclose any conflicts of interest.

Update from PAVE Lab Working Group

Dr. Koup reported that the goal of this working group is to arrive at consensus on procedures and avoid redundancies. Their December 2003 meeting reached consensus on blood processing, freezing and storage issues; an April 2004 teleconference considered T cell assay validations presented by HVTN and VRC. HVTN is currently standardizing the protocol for intracellular cytokine staining (ICS), which proved to be the most sensitive assay, and repeat proficiency tests are scheduled in June. Future tasks for HVTN are to establish criteria for positivity and to conduct precision studies and bridging studies for multiparameter analysis. Future tasks for the Lab Working Group are to address shipping, review the proficiency panel data, and discuss training at new sites. A workshop on peptides will be held in August or September.

In response to questions, Dr. Koup added that these results will be disseminated as widely as possible, first to PAVE members and then to vaccine development groups, with global dissemination through a website under discussion. The Lab Working Group is sponsored by PAVE, but NIAID pays for its meetings and other parties are welcome to participate, including ACTG, Pediatric ACTG, and EuroVacc.

Update from PAVE Site Development Working Group

Dr. Greenberg reported that a web-based survey was conducted in April and May 2004 to identify PAVE-sponsored sites, determine their capacity to conduct Phase 2B/3 trials, and define their needs for training and infrastructure to develop necessary operational capacity. Preliminary data are encouraging, identifying 24 sites in Latin America, Africa and Southeast Asia with considerable detail on staff, laboratory and data management capacity, target populations, and past studies. Data analysis will continue over the summer, and the working group has yet to formulate a plan to validate the data and prioritize responses. However, it appears that 12 of these sites will be ready for Phase 2B/3 trials in 2005-2008. The principal gaps at other sites include the lack of national vaccine plans, regulatory bodies, biosafety committees, communication plans, and community advisory boards.

In response to questions, Drs. Greenberg and Wasserheit added that all of the 24 sites have done some epidemiology and Phase 1 work in the past, but not all of them have experience in vaccine trials. There are questions about personnel at almost all of the sites, and the lack of senior staff can be a bigger barrier than lack of physical infrastructure at field sites. There is no preferred model for site development (e.g., stand alone, networked or partnered), and there is concern about creating too narrow a focus on vaccines rather than broader improvements in site capacity. This might be a topic for AVRWG to address in the future, and members eagerly await the development of priorities in this area by the Gates Enterprise. Members suggested efforts to encourage communication and collaboration across sites (e.g., within Kenya) and expedite the shipping of isolates from international sites to the PAVE laboratories and GenBank. The Site Development Working Group will update AVRWG as needed.

Clinical Plans for the Merck rAd Vaccine

Dr. Isaacs presented Merck's tentative plans for a Phase IIB clinical trial of their recombinant adenovirus (rAd)-based AIDS vaccine. The candidate vaccine uses a replication-defective adenovirus type 5 (Ad5) and targets the HIV gag, pol and nef proteins, major targets of T cell response that are highly conserved across clades. The monovalent (gag) version of this vaccine produced impressive results in rhesus monkeys.

Merck proposes a study to be carried out at sites where clade B HIV is prevalent. The protocol calls for a multicenter, randomized double-blind placebo controlled trial in 1500 patients age 18-45 with Ad5 titer under 200. Primary endpoint is whether the vaccine will prevent or alter infection; secondary endpoints are effect on viral set point, preservation of CD4+ counts, and duration of effect.

In response to questions, Dr. Isaacs added that the trial will recruit both homo- and heterosexual men and women, with particular attention to high-risk populations. Risk criteria are based on a number of factors. Members of AVRWG suggested that investigators monitor viral load throughout the trial, so as to measure degree of protection and efficacy as well as response. One member suggested that mathematical modeling of viral loads in acutely infected patients and subsequent set points could add precision to that aspect of the trial. One member suggested that the trial is not big enough to detect the primary endpoint, and another suggested that the trial should address the relationship between viral load and transmission. Nevertheless, it was the consensus of AVRWG that this trial should go forward.

DAIDS Decision-Making Process

Dr. Johnston outlined the priorities of the DAIDS vaccine research effort, which are to pursue fundamental knowledge that will inform vaccine design, to identify improved vaccine designs, and to advance the most promising candidates. It pursues these priorities through RO1 grants and solicited grant programs, as well as contracts to provide technical and logistical support for vaccine research and development. Partnerships and community involvement are central to these efforts, as is advice from external advisory groups. At the highest level are the OAR Advisory Group and NIAID Council, followed by the AIDS Research Advisory Committee (which advises on the design of solicited programs), the AVRWG (which provides ongoing technical and scientific advice), and the Prevention Sciences Review Committee (PSRC), (which oversees clinical trial protocols). In addition, most of the DAIDS grantees and contractors have their own advisory bodies.

Experience has shown that frequent input from these diverse sources contributes to the success of the effort, but Dr. Johnston would like to see additional input from other external groups and better coordination between the preclinical and clinical research advisory bodies. She would also like to have coordinated, proactive advice on the design of vaccine trials. She therefore proposed that, in addition to AVRWG, there be a Vaccine Development Resources Group to

advise on preclinical matters, and that the various DAIDS vaccine advisory groups have a biannual “summit” meeting.

Members indicated general agreement with this proposal, but they also suggested that their advice not be contingent on when the AVRWG holds its meetings. They also asked that, in future, the AVRWG be given more detailed information and more specific questions to answer, especially in regards to large-scale clinical trials, in advance of their meetings with DAIDS.

HVTN Guidelines for Moving Products to Phase 1, 2 and 3

Dr. Corey reported that HVTN seeks to establish a transparent, data-driven platform to assess vaccine safety and immunogenicity. At present they have both a scientific advisory committee and a laboratory advisory committee to work with the investigator to design a Phase 1 trial. The network's current portfolio includes about 3,500 subjects, split 60/40 between domestic and international trials. About 17 new protocols will be launched in the next 12 months, including DNA, pox virus, recombinant protein and peptide immunogens. Investigators anticipate that the acceptable threshold of immunogenicity will rise over time; other criteria for moving a candidate forward include primary isolate neutralization, increased safety, or major advantages in manufacturing or delivery. Responses other than increased immunogenicity that would justify additional work on T-cell candidates include:

- Novel T cell response;
- Quantification of T cell “memory pool;”
- Increased gamma interferon or IL-2 response;
- increased breadth of response (epitopes, strains, clades);
- More potent vectors;
- Combination vector approaches; and/or
- Multivalent inserts.

In the discussion that followed, members suggested that the ELISPOT assay is not a good measure of immunogenicity. Dr. Haynes summarized the discussion by identifying the following “hot topics” for increased, proactive investigation, including novel vectors, improved animal model systems, and improved neutralizing assays. He asked for members to form subgroups to address some or all of these topics, as well as how best to use the contract support and resources available from DAIDS.

Development Update on VRC DNA + rAd Vaccine

Dr. Nabel reported results from the VRC 004 clinical trial, which tested the DNA immunogen alone. The VRC 006 trial, which begins next week, is an FDA-approved Phase I trial of recombinant adenovirus. A proposed Phase III trial would enroll 15,000 subjects in a three-arm trial of placebo vs. rAd5 vs. DNA + rAd5. CD4 counts and viral load are the co-primary endpoints, and the size of the trial would allow investigators to capture the correlates of immunity should efficacy be shown. Future plans include a Phase IB trial by HVTN beginning 2004Q3, a Phase II trial in East Africa beginning in 2005Q1 or Q2, and a Phase III trial by PAVE beginning in 2006Q4 .

In response to questions, Dr. Nabel explained that support for the DNA prime came from animal studies. It remains to be seen whether DNA prime will overcome the dampening effect of preexisting Ad5 antibodies.

Gates Foundation Global HIV Vaccine Enterprise: Scientific Priorities

Dr. Esparza reviewed the history of the Enterprise, which was proposed in January 2003 as a mechanism to accelerate the development and evaluation of candidate vaccines by coordinating and optimizing international efforts. A steering committee met on May 17-18 in Washington, DC, to consolidate recommendations from working groups and lay out the principles, priorities and organization of the Enterprise. The Gates Foundation acted as convener only and expects to partner with other funding groups. Five areas of concentration have emerged:

1. Vaccine science and discovery (critical questions, novel mechanisms);
2. Immunological assays (development and standardization);
3. Vaccine development expertise and capabilities (personnel training and availability);
4. Clinical trial capacity (infrastructure development, fellowships and career awards); and
5. Information sharing and intellectual property issues.

In response to questions, Dr. Esparza added that the Enterprise is open to the entire world, but that NIH is expected to be a vital participant. The success of the Enterprise will depend in large part on stimulating new sources of funding to meet the expected shortfall in the next five years. Dr. Johnston indicated that AVRWG will be expected to comment not only on the scientific priorities of the Enterprise, but also on questions of coordination, joint RFAs, and how to respond to the Enterprise if additional funds are not forthcoming in NIH and NIAID budgets.

AIDS Vaccine Meetings

AVRWG discussed changing the frequency of domestic AIDS vaccine meetings from annual to biennial, on the odd-number years between the international AIDS conferences. Dr. Johnston suggested that this change would make things easier for OAR, and other participants noted that Keystone continues to be an annual event, although few international researchers come to Keystone. Members suggested doing more to bring Europeans to Keystone, or having a stronger vaccine content in the international meetings, or add a vaccine day at the annual Conference on Retroviruses and Opportunistic Infections (CROI). Consensus supported skipping the 2005 meeting and attempting to alternate the vaccine meeting and international AIDS meeting in future years.

Budget Presentation: AIDS and Vaccines

Dr. Bradac reported that the total HIV/AIDS research budgets of NIH and NIAID in FY 2004 were \$2.8 billion and \$1.3 billion. AIDS vaccine research received \$456 million, or 15.9 percent

of the NIH total, with three-quarters of this amount going to NIAID. Over the past 10 years, vaccine research has received an increasing share of total AIDS research spending, rising from 10 to 15 percent, with about half of that amount going to NIAID.

In the discussion that followed, members offered the following propositions: that vaccine research and development costs will rise sharply because of the candidates now in the pipeline; and a great deal of money is *not* being spent on AIDS vaccine development. Industry might spend \$250 million on manufacturing plants, but they are unlikely to spend that kind of money on clinical trials. Greater efficiencies might be possible through increased coordination and reduced redundancy, and new donors might be found, but it seems unlikely that the necessary funding will be available in the short to medium term.

Members suggested that it might be appropriate to do an update of the Levine Report of 1996, outlining the needs and probable costs of AIDS vaccine research. They agreed to write a letter to the OAR director, Dr. Whitescarver, to set that review in motion, and that this letter should focus narrowly on the increment required for advanced development.

Program Milestones Update

Dr. Bradac reported that ten Innovation Grants were awarded in the first two review cycles of FY04, and the third cycle is now pending. Candidate vaccines currently in the pipeline include 23 products. Given the continuing problems with MVA vaccines, the group asked whether it made sense to pursue all of the candidates currently in the pipeline.

Jorge Flores reported that there are 40 current or planned AIDS vaccine clinical trials being supported by DAIDS. USMHRP has nine clinical trials underway, and HVTN is conducting preparedness studies at new sites in six nations. A workshop was organized by the Vaccine Clinical Research Branch, held in April 2004, that addressed Endpoints and Regulatory Issues.

RV 144 Working Group Summary

Dr. Hammer presented the findings of his review (with Drs. Corey, Sadoff and Self) of scientific questions and protocol design of the RV 144 trial, recently launched in Thailand. This trial will enroll 16,000 healthy Thai adults in a trial of a combination vaccine – Aventis Pasteur’s ALVAC-HIV canarypox vector (vCP1521) plus VaxGen’s envelope glycoprotein gp120 (AIDSVAX), used in a prime-boost configuration – versus placebo. Primary endpoint is HIV infection; secondary endpoints are viral load and CD4 counts. An immunology sub-study will collect peripheral blood mononuclear cells (PBMCs) from 700 subjects at seven points during the study and follow-up. The review raised four principal questions that might improve this ongoing study:

1. *Should investigators switch endpoints?* By making ameliorization the co-primary endpoint, this might be able to reduce the sample size. If left as is, the current sample size will overpower the viremic endpoint.
2. *Should HIV-1 RNA and CD4+ counts be a composite endpoint?* Not necessarily, but viremic endpoints are crucial and require clearer definition. Investigators should have a detailed

analysis in place before the first PBMC collection.

3. *Should the study supply data to the DSMB in real time?* Yes, data from the 200-300 vaccinees and 100 controls, particularly T- cell counts, will provide information on activity of the vaccine during the trial.
4. *Should DSMB take an earlier look at interim efficacy or add a futility analysis?* No, the stopping guidelines are conservative and earlier analysis would provide no advantage. However, it would be reasonable to include a operational futility analysis.

In the discussion that followed, members asked whether the change in endpoint would require reconsent; apparently it would not. Reducing the sample size would save time but not money, and adding viremia endpoints would require a much longer follow-up. One member suggested that the analysis should include both the percentage that respond to the vaccine and the percentage that are actually protected by the vaccination. Most members seemed to favor the addition of the viremia endpoint. Dr. Johnston indicated that DAIDS would discuss the recommendations with USMHRP and the Thais, but that science rather than cost is the paramount consideration and DAIDS does not want to lose the acquisition endpoint. She will report back to AVRWG as decisions are made on this trial.

Wrap-Up

The next meeting of AVRWG after Lausanne will be in January 2005. Dr. Haynes will circulate an email on agenda topics for Lausanne, which might include presentations from EuroVacc and the Gates Enterprise.

Action Items

1. AVRWG asked that the PAVE update them as needed, particularly on analysis and validation of data from its survey of site capacity. AVRWG also expressed interest in having PAVE coordinate and facilitate the collection and circulation of isolates from field sites.
2. The sense of AVRWG was that the Merck rAd trial should go forward. They suggested that viral set point should be a secondary end point, and viral load should be monitored throughout the trial.
3. Members asked that, if they are to provide DAIDS with proactive advice on vaccine research, they should be given more detailed information in advance of meetings, including the specific scientific questions they are being asked to address.
4. AVRWG to sponsor a day-long workshop on persistent vectors to be held during the fall at NIH. Members will communicate with Dr. Haynes about organization and content; possible topics include persistent vectors that have not been evaluated thoroughly, including CMV, Epstein-Barr, and herpes.
5. A subcommittee will examine and report back on the topic of how to restructure and make use of the Vaccine Development Resource Group: Drs. Corey, Emini, and Sadoff.
6. AVRWG accepts the idea of having international meetings every other year, beginning in 2006, alternating with the AIDS Congress in odd-numbered years. It will be important to coordinate this change with the European Union. Drs. Korber, Goldenthal, Greenberg, Richman, and Hunter volunteered to begin planning the 2006 meeting.

7. AVRWG will draft a letter to Jack Whitescarver, Director of OAR, asking for an update of the 1996 Levine Report, or at least a careful audit of spending by NIH institutes other than NIAID that is coded as vaccine research and development.
8. It was the sense of AVRWG that the RV-144 trial should be modified to make amelioration of viremia a co-primary endpoint, to provide immunology data to the DSMB in real time, and to consider conducting a futility analysis. DAIDS will discuss this recommendation with USMHRP and the Thais, and Dr. Johnston will report back to AVRWG on the decisions they make. AVRWG will conduct additional review on this trial, with Dr. Wakefield joining the existing RV-144 Working Group.
9. Dr. Haynes will send committee members an organizing email on the Lausanne meeting. Possible agenda topics include EuroVacc, the Enterprise, and how to revise the AVRWG report on vaccine research priorities.